DATA EVALUATION RECORD

ETHABOXAM/090205
[OPPTS (§ 870.3100)]

SUBCHRONIC ORAL TOXICITY STUDY - RODENT
MRID 46387805

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
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Task Order No. 103-2005

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DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity- rat [OPPTS 870.3100 (§82-1a)] rat OECD 408.

PC CODE: 090205 **DP BARCODE:** D313732

TEST MATERIAL (PURITY): Ethaboxam (LGC-30473, 99.2% a.i.)

SYNONYMS: *(RS)-N*-(α-cyano-2-thenyl)-4-ethyl-2-(ethylamino)-1,3-thiazole-5-carboxamide;

CITATION: P. Higgs, (1997) LGC-30473. Toxicity to rats by dietary administration for 13 weeks. Huntingdon Life Sciences Ltd., Woolley Road, Alconbury, Huntingdon, Cambridgeshire, PE18 6ES, England. Project No. LKY 26/963670. June 27, 1997. MRID 46387805. Unpublished.

SPONSOR: LG Chemical Lt./Research Park, Specialty Chemical Research Institute, 104-1, Moonji-dong, Yusung-gu, Taejon, 305-380, Korea.

EXECUTIVE SUMMARY: In a 13-week oral toxicity study (MRID 46387805), Ethaboxam (LGC-30473, 99.2% a.i.) was administered to 10 Crl:CD BR rats/sex/dose in the diet at concentrations of 0, 200, 650, or 2000 ppm (approximately equivalent to 0, 16.3, 49.7, and 154 mg/kg/day males, and 0, 17.9, 58.0, and 164 mg/kg/day females).

By study end, 7/10 high-dose female rats had developed alopecia. No alopecia was found in the control group or other treatment groups. The body weight of high-dose male and female groups was significantly decreased within one week of treatment and remained decreased throughout the study. Total body weight gain of the high-dose male and female rats for the study was ~67% of their respective control groups. This was accompanied by an ~20% decrease in food consumption.

No significant treatment-related effects were found on mortality, hematology, opthalmoscopic, or urinalysis parameters. An increased relative liver weight (to body weight) of high-dose male and female rats and centrilobular hypertrophy was found in most high-dose male and female rats. Fine vacuolation of the adrenal *zona glomerulosa* observed in 3/10 high-dose males and 8/10 high-dose females was not observed in any other group.

Severe testicular atrophy and interstitial cell hyperplasia were noted in most high-dose rats. There were no spermatozoa found in the epididymides of high-dose rats and abnormal spermatogenic cells were found in some of the ducts. In rats at 650 ppm, abnormal spermatids

were found in the testes of 4/10 rats, and abnormal spermatogenic cells were found in the epididymal ducts of 6/10 rats.

The LOAEL for males is 650 ppm (49.7 mg/kg/day) based on testicular/epididymal effects (abnormal spermatids in the testes, abnormal spermatogenic cells in epididymal ducts). The LOAEL for females is 2000 ppm (164 mg/kg/day) based on fine vacuolation of the adrenal *zona glomerulosa*, and lower body weights. The NOAELs for males and females are 200 ppm (16.3 mg/kg/day) and 650 ppm (58 mg/kg/day), respectively.

The 13-week oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement (OPPTS 870.3100; OECD 408) for a 90-day oral toxicity study in rats.

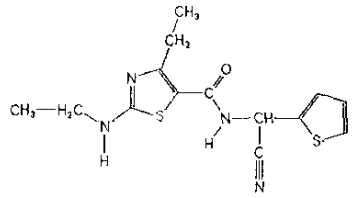
COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: LGC-30473

Description:	creamy white powder
Lot/Batch #:	6-1
Purity	99.2% a.i.
Compound Stability:	Not provided (Formulations stable for 22 days at room temperature; test material stable for duration of study)
CAS No. of TGAI:	162650-77-3
Structure:	



2. Vehicle and/or positive control: Diet

3. Test animals:

Species:	Rat	
Strain:	Crl:CD BR	
Age/weight at study initiation:	~6 weeks; males 168-201 g; females 145-178 g	
Source:	Charles River UK, Ltd, Margate, Kent, England	
Housing:	5 of the same sex/suspended cages	
Diet:	SDS Rat and Mouse No. 1 maintenance diet, *ad libitum*	
Water:	tap water, *ad libitum* (water bottles)	
Environmental conditions:	**Temperature:**	18-23°C
	Humidity:	44-66%
	Air changes:	not reported
	Photoperiod:	12 hrs light/dark
Acclimation period:	~2 weeks	

B. STUDY DESIGN:

1. **In life dates**: Start: August 28, 1996; End: November 27-28, 1996

2. **Animal assignment**: Animals were assigned randomly based on body weight to the test groups noted in Table 1.

TABLE 1: Study design

Test group	Conc. in diet (ppm)	Dose to animal (mg/kg/day)	No. Male	No. Female
Control	0	–	10	10
Low	200	16.3♂ / 17.9 ♀	10	10
Mid	650	49.7 ♂ / 58.0 ♀	10	10
High	2000	154 ♂ / 164 ♀	10	10

Data from page 25, MRID 46387805

3. **Dose selection rationale:** A dose selection rationale was not provided.

4. **Diet preparation and analysis:** Diets were prepared weekly by adding the appropriate amount of test material to SDS Rat and Mouse No. 1 maintenance diet to prepare a premix. The test diets were prepared by diluting the premix with untreated diet which was mixed for at least five minutes. Dietary stability and homogeneity studies were previously conducted and reported in Study Report No. LKY 51/962291. Diet concentration analyses were done on diets prepared during weeks 1 and 11 of the study.

Results:

Homogeneity analysis: Not reported in MRID 46387805 but included in Study Report No. LKY 51/962291.

Stability analysis: Not reported in MRID 46387805 but included in Study Report No. LKY 51/962291.

Concentration analysis: All diets prepared during Weeks 1 and 11 of the study were within 3% of the nominal concentration.

5. **Statistics**: Bartlett's test was done to determine the homogeneity of the data. If significant at the 1% level, logarithmic data transformations were done. If the data were homogeneous, ANOVA was done, otherwise the data were analyzed by the Kruskal-Wallis method. Significant ANOVA results were followed by the Williams' test to determine between group differences. Heterogenous differences between groups were determined by the method described by Shirley (1977). For organ weight data, ANCOVA was used with the terminal body weight as the co-variant when within-group differences exceeded the 10% level.

C. METHODS:

1. Observations:

1a. **Cageside observations:** During the first five weeks of treatment, the animals were observed for clinical signs of toxicity, behavioral changes, and were palpated once daily 5 days/week. After that, all animals were observed at least weekly through the remainder of the study.

1b. **Clinical examinations:** The animals were observed for mortality twice daily 5 days/week and once daily during the weekends.

1c. **Neurological evaluations:** Neurological evaluations, other than behavior, were not done.

2. **Body weight:** The body weight of each animal was measured at the start of the study and weekly thereafter.

3. **Food and water consumption and compound intake:** Food consumed by each cage of animals was recorded weekly. Food intake per rat was calculated using the amount of food given to and left by each cage and the number of rats in the cage. When possible, food conversion ratios were calculated from the body weight and food consumption data as weight of food consumed per unit gain in body weight.

   Water consumption was visually examined daily and was measured by weight over daily periods during week 12.

   Compound consumption was calculated each week from the group mean body weight gain, the food consumed, and the test material diet concentration.

4. **Ophthalmoscopic examination:** The eyes of all rats included in the study were examined before assignment to treatment groups. At week 12, the eyes of control and high-dose rats were again examined.

5. **Hematology and clinical chemistry:** During week 13 of the study, fasted blood was drawn under light ether anesthesia from the orbital sinus of all rats in the study. The blood samples were collected in EDTA for hematological analysis, citrate for coagulation analyses, and heparin for clinical chemistry analyses. The CHECKED (X) parameters were examined.

a. Hematology:

x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)*
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)*
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)*
x	Platelet count*	-	Reticulocyte count
-	Blood clotting measurements*	x	Activated Partial Thromboplastin Time
x	(Thromboplastin time)		
-	(Clotting time)		
x	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
- Not examined

b. Clinical chemistry:

	ELECTROLYTES		OTHER
x	Calcium	x	Albumin*
x	Chloride	x	Creatinine*
-	Magnesium	x	Urea nitrogen*
x	Phosphorus	x	Total Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	ENZYMES (more than 2 hepatic enzymes)*		
		-	Total bilirubin
x	Alkaline phosphatase (ALK)*	x	Total protein (TP)*
-	Cholinesterase (ChE)	-	Triglycerides
-	Creatine phosphokinase	-	Serum protein electrophoresis
-	Lactic acid dehydrogenase (LDH)		
x	Alanine aminotransferase (ALT/also SGPT)*		
x	Aspartate aminotransferase (AST/also SGOT)*		
-	Sorbitol dehydrogenase*		
-	Gamma glutamyl transferase (GGT)*		
-	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
- Not examined

6. **Urinalysis**[1]: Overnight urine samples were collected during week 13 from fasted (water removed) animals. The CHECKED (X) parameters were examined.

-	Appearance*	x	Glucose
x	Volume*	x	Ketones
x	Specific gravity/osmolality*	x	Bilirubin
x	pH*	x	Blood/blood cells*
x	Sediment (microscopic)	-	Nitrate
x	Protein*	x	Urobilinogen

[1] Optional for 90-day oral rodent studies
* Recommended for 90-day oral rodent studies
- Not examined

7. **Sacrifice and pathology**: All animals that died and those sacrificed on schedule (carbon dioxide asphyxiation) were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were

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weighed. Histological examinations were performed on the following tissues: adrenals, gastrointestinal tract, brain, epididymides, eyes, heart, kidneys, liver, lungs, mammary gland, abnormal tissues, ovaries, pancreas, pituitary, prostate, salivary gland, spinal cord, spleen, bone/marrow, testes, thymus, thyroid/parathyroid, trachea, urinary bladder, and uterus.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*+
x	Salivary glands*	xx	Heart*+	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	xx	Pituitary*
x	Duodenum*	xx	Spleen*+	x	Eyes (optic nerve)*
x	Jejunum*	x	Thymus*+		GLANDULAR
x	Ileum*			xx	Adrenal gland*+
x	Cecum*		UROGENITAL	x	Lacrimal gland
x	Colon*	xx	Kidneys*+	x	Parathyroid*
x	Rectum*	x	Urinary bladder*	xx	Thyroid*
xx	Liver*+	xx	Testes*+		OTHER
-	*Gall bladder (not rat)**	xx	*Epididymides*+*	x	*Bone (sternum and/or femur)*
-	Bile duct (rat)	xx	Prostate*	x	Skeletal muscle
x	Pancreas*	xx	Seminal vesicles*	x	Skin*
	RESPIRATORY	x	Ovaries*+	x	All gross lesions and masses*
x	Trachea*	xx	Uterus*+	x	Harderian gland
xx	Lung*	x	Mammary gland*	x	Head including nasal cavity, paranasal sinus, oral cavity, nasopharynx, middle ear, teeth, and Zymbal gland.
x	Nose*	x	Vagina		
x	Pharynx*				
x	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
\+ Organ weights required for rodent studies.
\- Not collected

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity:** The only clinical sign of toxicity noted was an increased incidence of alopecia in female high-dose rats (7/10 vs 0/10 control from week 3 to the end of the study). Yellow stained litter paper was noted under cages of all treated rats.

2. **Mortality**: No unscheduled deaths were reported.

3. **Neurological evaluations**: No behavioral changes were noted. Other neurological studies were not done.

B. BODY WEIGHT AND WEIGHT GAIN: As shown in Table 2, the body weight of high-dose male and female rats was statistically decreased (16-21%) from week one through the remainder of the study. Total body weight gain was decreased in mid- dose males (12%) and high-dose males and high-dose females (31% and 35%, respectively) at the termination of the study.

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TABLE 2. Average body weight and body weight gain (± S.D.) during 13 weeks of treatment[a]						
Concentration [ppm]	Body weight (g)				Total weight gain	
	Week -1	Week 1	Week 7	Week 13	g	% of control
Male						
0	129	244 ± 12.5	447 ± 25.6	502 ± 36.9	316 ± 33	-
Low (200)	129	245 ± 11.6 (100)	457 ± 29.2 (102)	511 ± 36.8 (102)	322 ± 37	102
Mid (650)	129	237 ± 10.4 (97)	422 ± 32.9 (94)	468 ± 47.7 (93)	280 ± 46*	88
High (2000)	129	210*** ± 11.2 (86)	360*** ± 25.2 (81)	397*** ± 36.8 (79)	218 ± 33**	69
Female						
0	122	183 ± 7.83	266 ± 15.7	282 ± 25.8	124 ± 22	-
Low (200)	122	187 ± 12.5 (102)	276 ± 19.8 (104)	294 ± 21.6 (104)	132 ± 18	107
Mid (650)	122	183 ± 14.3 (100)	271 ± 15.6 (102)	285 ± 24.1(101)	123 ± 17	100
High (2000)	122	164** ± 7.4 (89)	227*** ± 11.7 (85)	237*** ± 11.5 (84)	81 ± 10**	65

[a] Data from page 24 and 26 and calculated from Appendix 1 pages 62-65 of MRID 46387805.
Results in parentheses are percent of control calculated by reviewer.
*p <0.05; **p <0.01; ***p<0.001

C. FOOD CONSUMPTION AND COMPOUND INTAKE:

1. **Food consumption**: Total food consumption was decreased 18% in males and 22% in females of the high-dose group for the entire duration of the study. No other significant decreases in food consumption were noted in the other groups.

2. **Compound consumption**: Test material consumption is shown in Table 1.

3. **Food efficiency**: The food efficiency of high-dose male and female rats was decreased ~19% throughout the study. No other effects were noted on food efficiency in the other groups.

4. **Water consumption**: Measured water consumption at week 12 showed that 2000 ppm males and females consumed less water than did the respective controls or lower dose rats. At 200, 650, and 2000 ppm, there were percent changes from controls as follows: males = ↑15, ↓6, and ↓7; females = ↓15, ↓16, and ↓38. The decreases were concomitant with lower food consumption (lower group mean body weights).

D. OPHTHALMOSCOPIC EXAMINATION: No treatment-related effects were found.

E. BLOOD ANALYSES:

1. **Hematology:** Although some slight changes were noted in hematological parameters, none were biologically or toxicologically relevant.

2. **Clinical chemistry:** Although some slight changes were noted in clinical chemistry parameters, none were biologically or toxicologically relevant. Slight increases in AP

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activity (9% and 32%) and cholesterol (49% and 43%) were found in high-dose male and female rats, respectively.

F. URINALYSIS: No biologically or toxicologically significant effects were noted

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** The relative liver weights of male and female rats at 2000 ppm and female rats at 650 ppm were significantly increased and correlated with microscopic findings. However, these increases were likely due to the lower terminal body weights compared with controls. For females at 650 ppm, although the absolute organ weight was greater than the control value, this effect was not observed at 2000 ppm. The absolute and/or relative weight of the testes, seminal vesicles, prostate, and epididymides of high-dose rats were significantly decreased. Also, the epididymal weight of rats treated with 650 ppm was decreased. These effects on male reproductive organs were correlated with histopathological effects. No treatment-related effects were noted in the uterus or ovaries of treated female rats.

TABLE 3. Selected organ absolute (g) and covariant (to body weight, g) weight of male and female rats treated with LGC-30473 for 13 weeks

Organ/tissue		Male				Female			
		0 ppm	200 ppm	650 ppm	2000 ppm	0 ppm	200 ppm	650 ppm	2000 ppm
Body	Absolute	496	508	464	394	282	292	286	239
Lung	Absolute	1.78	1.79	1.86	1.94	1.32	1.47	1.61	1.48
Liver	Absolute	21.1	22.3	19.4	18.8	10.5	11.7	12.0	10.5
	Covariant	19.5	19.5	19.4	22.8*	10.2	10.9	11.5**	12.1**
Prostate	Absolute	0.940	1.077	0.979	0.787*	–	–	–	–
Left Testis	Absolute	1.804	1.830	1.833	0.861	–	–	–	–
	Covariant	1.758	1.767	1.834	0.969**				
Right Testis	Absolute	1.808	1.810	1.849	0.803**	–	–	–	–
Seminal Vesicle	Abs.	1.46	1.50	1.34	1.18	–	–	–	–
L. Epididymides	Abs.	0.642	0.676	0.590	0.361**	–	–	–	–
R. Epididymides	Abs.	0.683	0.684	0.594**	0.363**	–	–	–	–
Uterus	Absolute	–	–	–	–	0.54	0.65	0.57	0.52
Ovaries	Absolute	–	–	–	–	78.8	69.1	74.0	71.6

Data from Table 10, pages 46-49 of MRID 46387805
*p≤0.05; **p≤0.01

2. **Gross pathology**: At necropsy, all male rats in the high-dose group had small, blue testes and small epididymides. These were not observed in control rats or in rats of other treatment groups. Three female rats of the high-dose group had a small and/or fluid distention of the uterus. The uterine effects were not found in control rats or confirmed histologically. Several male and female rats that received 650 ppm or 2000 ppm and several female rats that received 200 ppm had congested lungs at necropsy. The congestion of male rats was correlated to the increased lung weight (Table 3) but no correlation existed for female rats. No toxicological significance was attached to the congestion.

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3. **Microscopic pathology**: Hepatocyte centrilobular hypertrophy was found in all high-dose males and 8/10 high-dose female rats. This was not observed in any other treatment groups. Fine vacuolation of the adrenal *zona glomerulosa* was observed in 3/10 high-dose males and 8/10 high-dose female rats but not in any other treatment group or controls. Severe testicular atrophy was observed in all high-dose male rats. This was accompanied by testicular interstitial hyperplasia (8/10), the absence of spermatozoa in the epididymides (10/10), and occasional abnormal spermatogenic cells in epididymal ducts of 8/10 high-dose rats (0/10 for control). Abnormal spermatids were observed in the testes of 4/10 male rats treated with 650 ppm and abnormal spermatogenic cells were seen in the epididymal ducts of 6/10 rats. These changes account for the decreased testes and/or epididymal weight of mid- and high-dose rats. No other microscopic treatment-related effects were observed.

TABLE 4. Incidence of microscopic lesions in male and female rats treated with LGC-30473 for 13 weeks

Organ/tissue	Male				Female			
	0 ppm	200 ppm	650 ppm	2000 ppm	0 ppm	200 ppm	650 ppm	2000 ppm
Liver								
Centrilobular hypertrophy	0/10	0/10	0/10	10/10**	0/10	0/10	0/10	8/10**
Adrenal								
Fine vacuolation of *zona glomerulosa*	0/10	0/10	0/10	3/10	0/10	0/10	0/10	8/10**
Testes								
Severe atrophy	0/10	0/10	0/10	10/10**	–	–	–	–
Abnormal spermatids	0/10	0/10	4/10*	0/10				
Interstitial cell hyperplasia	0/10	0/10	0/10	8/10**				
Epididymides								
Absent spermatozoa	0/10	0/10	0/10	10/10**	–	–	–	–
Abnormal spermatogenic cells occasionally seen in ducts	0/10	0/10	1/10	8/10**				
Abnormal spermatogenic cells in ducts	0/10	0/10	6/10**	0/10				

Data from pages 29-30 of MRID 46387805
*p≤0.05; **p≤0.01

III. DISCUSSION AND CONCLUSIONS:

A. **INVESTIGATORS' CONCLUSIONS:** The study author concluded that treatment of male and female rats with 2000 ppm LGC-30473 decreased the body weight, food intake, and food efficiency. Although treatment with the test material slightly affected some hematological, clinical chemistry, and urinalysis parameters, none were of toxicological significance. Treatment with the test material increased the absolute and relative (to body weight) of the liver, an effect associated microscopically with centrilobular hypertrophy. Vacuolation of the adrenal *zona glomerulosa* was noted particularly in high-dose female rats. Gross observations at necropsy (decreased organ weights and macropathology) were diagnosed histologically as a graded response consisting of severe testicular atrophy at 2000 ppm and abnormal spermatids occasionally seen in the tubules of 650 ppm rats, both associated with changes in the epididymides. No treatment-related effects were found in males at 200 ppm or in females at 650 ppm.

B. REVIEWER COMMENTS: In this study, groups of 10 male and 10 female rats were treated with 0, 200, 650, or 2000 ppm LGC-30473 in the diet for 13 weeks. Within a week of treatment, several female rats in the high-dose group developed alopecia which progressed to 7/10 by study end. No alopecia was found on the control or other treatment groups. The body weight of high-dose male and female groups was significantly decreased ($p < 0.01$ or 0.001) within one week of treatment and remained decreased throughout the study (males = 14-21%; females = 11-16%). Total body weight gain of the high-dose male and female rats in the study was ~67% of their respective control groups. This was accompanied by an ~20% decrease in food consumption and a decrease in food utilization. The decreased food utilization of high-dose males and females suggests that toxicity rather than food palatability was responsible for the decreased body weight and body weight gain. Measured water consumption at week 12 indicated that less water was consumed by the high-dose animals of both sexes. This observation was accompanied by lower food intake and lower body weight/gains compared with the controls and lower dose groups.

No significant treatment-related effects were found on mortality, hematology, opthalmoscopic, or urinalysis parameters. Although treatment-related changes were observed in some clinical chemistry parameters, none were biologically relevant. Slight increases in AP activity and cholesterol, a sign of slight hepatic congestion, were consistent with the increased covariant liver weight of high-dose male and female rats and the 10/10 and 8/10 incidence of centrilobular hypertrophy found in high-dose male and female rats, respectively. Fine vacuolation of the adrenal *zona glomerulosa* in 3/10 high-dose male and 8/10 high-dose female groups but was not observed in any other group. The toxicological significance of this is unclear.

The most notable effects of treatment with LGC-30473 were to the male reproductive system. Severe testicular atrophy was noted in all high-dose rats; with interstitial cell hyperplasia observed in 8/10. There were no spermatozoa found in the epididymides of high-dose rats and abnormal spermatogenic cells were found in some of the ducts. In rats treated with 650 ppm test material, abnormal spermatids were found in the testes of 4/10 rats, and abnormal spermatogenic cells were found in the epididymal ducts of 6/10 rats.

The LOAEL for males is 650 ppm (49.7 mg/kg/day) based on testicular/epididymal effects (abnormal spermatids in the testes, abnormal spermatogenic cells in epididymal ducts). The LOAEL for females is 2000 ppm (164 mg/kg/day) based on fine vacuolation of the adrenal *zona glomerulosa*, and lower body weights. The NOAELs for males and females are 200 ppm (16.3 mg/kg/day) and 650 ppm (58 mg/kg/day), respectively.

C. STUDY DEFICIENCIES: None that would invalidate the study results.

DATA FOR ENTRY INTO ISIS

Subchronic (90 day) Oral Study - rodents (870.3100)

PC code	MRID	Study	Species	Duration	Route	Admin	Dose range mg/kg/day	Doses mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ	Comments
090205	46387805	subchronic	rat	13 weeks	oral	dietary	♂ 16.3-154 ♀ 17.9-164	♂ 16.3, 49.7, 154 ♀ 17.9,58.0, 164	♂ 16.3 ♀ 58.0	♂ 49.7 ♀ 164	♂ Testes, epididymides ♀ Adrenal gland, body wt, wt. gain	Toxicity